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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,302	PERBELLINI ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-49* is/are pending in the application.

4a) Of the above claim(s) *44-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 29-43, in the reply filed on 10/3/08 is acknowledged. The traversal is on the ground(s) that the inventions share unity. This is not found persuasive because the methods in claims 44 and 45 do not use the product made by the method of claim 29 as claimed. Claim 29 places no limit on the substitution degree of hyaluronic acid with retinoic acid, so the methods do not share scope. The requirement is still deemed proper and is therefore made FINAL.

Applicant's election with traverse of various species in the reply filed on 10/3/08 is acknowledged. The traversal is on the ground(s) that the species possess unity of invention. The examiner agrees and withdraws the requirement for an election of species.

Claims 44-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/3/08.

Examination on the merits will commence at this time on claims 29-43 ONLY.

Claim Objections

Claims 36, 37, and 39 are objected to because of various informalities. Claim 36 formats the scientific name *Homo sapiens* incorrectly. Taxonomic distinctions should be placed in italics, and the entire genus should be written out in the first recitation. Applicant may wish to replace “H. sapiens” with “humans.” Claim 37 recites an

extraneous word ("of") at line 2. Claim 39 incorrectly formats the Latin phrases *in vitro* and *ex vivo*. These and all foreign phrases should be placed in italics. Appropriate correction of these issues is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for differentiating cardiomyocytes from a few types of stem cells with a few retinoic acid esters of hyaluronic acid, does not reasonably provide enablement for differentiating cardiomyocytes from every kind of stem cell by contacting the cell with any retinoic acid ester of hyaluronic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Claim 29 is interpreted for this rejection (see indefiniteness rejections below) as being drawn to a method of differentiating cardiomyocytes comprising contacting stem cells with a retinoic ester of hyaluronic acid (HRE) and, optionally, selecting cardiomyocytes from the resulting culture; claim 39 is interpreted as being drawn to a therapeutic method for using the cells produced by the method of claim 29. Some claims attempt to further limit the HREs (claims 30-32 and 40) and some claims limit the stem cells (claims 33 and 35-38). While claims 30-32 and 40 address some characteristics of the HREs, the disclosure as a whole fails to sufficiently describe the structure such that the skilled artisan could have identified all of the HREs capable of promoting myocardial differentiation of stem cells without undue experimentation.

It is noted that the specification provides only a cursory description of the HREs. At page 3, the HREs are described as such:

> The esters of the invention are partially or totally esterified with retinoic acid. When hyaluronic acid is not completely esterified with retinoic acid, it can be esterified with other short chain alkanoic acids, as for instance propanoic acid or butyric acid, the latter being preferred.
>
> Moreover, the esters have preferably a molecular weight ranging between 10.000 [sic] and 30.000 [sic] Daltons: it is meant that such "molecular weight" refers to the average molecular weight (MW) of hyaluronic acid alone, without considering the contribution of butyric and retinoic residues.

However, this portion of the specification does not address the specific structure of the HREs, and the specification also fails to detail any process by which HREs useful for the claimed methods could be prepared. The working examples merely refer to the HREs generally, not by any structural or chemical properties.

Retinoic acid (RA) derivatives were well known in the art at the time of filing, as were hyaluronic acid (HA) derivatives. However, both of these compounds are highly reactive, and preparing HREs with the claimed properties would have required undue experimentation at the time of filing. Pouyani et al. (1997, U.S. Patent 5,652,347; reference A) teaches methods for functionalizing HA with other active groups. Pouyani teaches that HA is a polymer of repeating disaccharide units (column 1, lines 13-15, and structure at column 1). The structure depicted by Pouyani illustrates the extremely high number of reactive groups within HA (i.e., all of the -OH hydroxyl and –COOH carboxyl groups), the latter of which may be esterified to varying degrees. Maier et al. (1997, U.S. Patent 5,674,852; reference B) teaches that RA is also a reactive molecule that may be esterified to saccharide backbones (see columns 1 and 2 and generally Maier). In other words, given the highly reactive nature of both HA and RA, the scope of "retinoic acid esters of hyaluronic acid" is sufficiently broad that the skilled artisan could not necessarily have predicted the structure of those compounds or the degree of esterification necessary to produce HREs capable of promoting myocardial differentiation of stem cells.

Rastrelli et al. (2005, U.S. Patent 6,897,203; reference C) teach methods for functionalizing HA with RA by esterifying the two to varying degrees (see the Examples at columns 6-10) and establish that some of these compositions promote cardiomyogenesis in P19 cells, a mammalian teratocarcinoma line capable of differentiating into cardiomyocytes (Example 10 at column 11). However, it is noted that the P19 cells of Rastrelli are not stem cells per se, and more importantly, the teachings

of Rastrelli are not incorporated by reference into the instant specification or even mentioned in its text. It would be unreasonable, therefore, to limit the HREs of the instant claims to those taught by Rastrelli or even to apply the teachings of Rastrelli as potentially enabling regarding the instant claims, which specifically address differentiating stem cells.

Furthermore, the scope of the stem cells supported by the disclosure as being suitable for the method of claim 29 is far narrower than the claimed scope. The working examples are limited entirely to GTR1 cells, which are a modified embryonic stem cell line pre-selected for a tendency toward cardiomyogenesis by their expression of puromycin resistance from a myosin heavy chain promoter (page 13, first full paragraph under Example 1). The specification does not appear to include any working examples in which any other type of stem cell is contacted with any HRE.

The genus of stem cells is broad and diverse, including pluripotent embryonic stem cells and multipotent mesenchymal stem cells (MSCs), which can be obtained from bone marrow and adipose tissue, e.g. Furthermore, hematopoietic stem cells (HSCs) are a relatively narrow genus of stem cells that are capable of differentiating into all types of blood cells but, under normal conditions, no other types of cells. Each of these cell types has acquired its own status in the art because the effect of a particular active agent on one type of these cells is not generally predictive of the same agent's effect on another type.

For example, transforming growth factor beta (TGF-b) is a growth factor with diverse effects on different stem cell types. Kumar et al. (2005, *Biochemical and*

Biophysical Research Communications 332: 135-141; reference U) teach that embryonic stem cells treated with TGF-b respond by forming embryoid bodies and then differentiating into smooth muscle or cardiomyocytes (page 139, e.g.). Longobardi et al. (2006, *Journal of Mineral and Bone Research* 21: 626-636; reference V) teach that MSCs treated with TGF-b respond by differentiating to chondrocytes (page 626). Liao (2005, *Circulation* 111: 2416-2417; reference W) teaches that HSCs treated with TGF-b can transdifferentiate to yield cardiomyocytes (page 2417). The varying effects of a single growth factor on these different types of cells illustrates that they are not functional equivalents for each other, so predicting the effect of a given active agent on one type based on its effect on another type would have been impossible at the time of the invention.

M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254,

70 USPQ2d 1321, 1326 (Fed. Cir. 2004)…In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." As the above discussion illustrates, the effects of active agents on different kinds of stem cells were unpredictable at the time of the invention, so this art must be considered "nascent," and the amount of guidance required is therefore relatively high. The fact that the disclosure broadly speculates that other cells may serve as the starting material (see page 7, paragraph 4, of the as-filed specification) cannot be considered an enabling disclosure, given the unpredictable nature of this art.

In summary, the working examples are limited to a few in which one stem cell type that is predisposed to differentiate into cardiomyocytes is contacted with some undefined HREs for some undisclosed time, thereby yielding cardiomyocytes. The specification is completely silent as to the structure and preparation of the HREs and includes no specific guidance for identifying conditions under which any stem cell other than GRT1 cells could be differentiated to cardiomyocytes using any HREs. While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Generally, the claims do not employ phrasing standard in prosecution in the USPTO. Applicant is urged to refer to allowed patent claims in choosing transitional phrases, constructing Markush language, and formatting foreign phrases. Applicant is encouraged to amend the claims such that they conform to accepted practice.

Claims 29-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is drawn to a process for preparing cardiomyocytes from stem cells "comprising essentially an incubation of said stem cells," which is confusing for several reasons. The transitional phrase "comprising essentially" is not a generally accepted phrase in PTO practice. M.P.E.P. § 2111.03 distinguishes between "comprising" and "consisting essentially of" but makes no provision for "comprising essentially." It is not clear which steps may be added to the method or omitted from the method while maintaining the scope of the claims. The issue is further clouded by the presence of "optional" elements in the method (i.e., the optional selection at lines 3-4). The metes and bounds of the claimed method are not particularly pointed out. Furthermore, it is not clear that the claim limitation "an incubation" is an active method step. The claim should be redrafted such that it clearly indicates which steps are included in the method and which may not be included. Clarification is required.

Claim 29 is further queried because the steps within the claim do not appear to lead necessarily to the end point recited in the preamble. The preamble to claim 29

indicates that differentiated cardiomyocytes are produced, but all that is **required** in claim 29 is an incubation with some amount of some retinoic ester of hyaluronic acid for some unspecified amount of time. The claim does not require, for example, incubating the stem cells with the HRE until cardiomyocytes form. Clarification is required.

Because claims 30-43 depend from indefinite claim 29 and do not clarify these point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 30 requires that the esters of claim 29 have a substitution degree "comprised from 0.00001 to 0.5," the phrasing of which is queried. Again, "comprised" is open-claim language, so the limitation does not concretely narrow the previous claim. If applicant intends to require that the substitution degree range between 0.00001 and 0.5, the claim should recite such (as in claim 32, e.g.). Claim 40 suffers similar deficiencies. Clarification is required.

Claim 31 recites the phrase "mixed esters," which is queried.

Claim 32 requires a "ratio between the degree of substitution with butyric acid and retinoic acid … of at least 6," but it is not clear whether this ratio is one comparing two different degrees of substitution or one comparing the degree of substitution with butyric acid to, e.g., the amount of retinoic acid. Clarification is required.

Claim 33 requires that the stem cells be "autologous or heterologous," but the claim provides no basis for these relative terms. Claim 39 suffers similar deficiencies. Clarification is required.

Claim 34 recites the phrase "gene-trapping" in quotation marks, indicating that the means employed is not gene-trapping per se, but rather some variation thereon.

Clarification is required. The quotation marks should be removed and the claim amended to particularly recite any essential modification to the art-accepted method of gene-trapping.

Claim 36 is in improper Markush form; a Markush group should be in the form "an agent selected from the group consisting of A, B, **and** C". Currently, it is not clear which species are included in the Markush group and which are not and whether the list was meant to continue, including additional species. Clarification is required.

Claim 38 is also in improper Markush form; a Markush group should be in the form "an agent selected **from** the group consisting of A, B, **and** C". Currently, it is not clear which species are included in the Markush group and which are not and whether the list was meant to continue, including additional species. Clarification is required.

Claim 39 is confusing because the preamble is drawn to a therapeutic method, but the steps do not include any step in which any active agent is administered to the patient in need of treatment. Clarification is required.

Claim 39 recites the phrases "*in vitro*" and "*ex vivo*" in quotation marks, indicating that the differentiation does not occur *in vitro* or *ex vivo* per se, but rather some variation thereon. Clarification is required. The quotation marks should be removed and the claim amended to particularly recite the conditions of the differentiation if necessary.

Claim 41 recites "re-implantation," which implies that a first implantation step has taken place, but no such step is recited in the claims. This claim should be amended such that its relationship to the method steps of the other claims is particularly pointed out. Clarification is required.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651